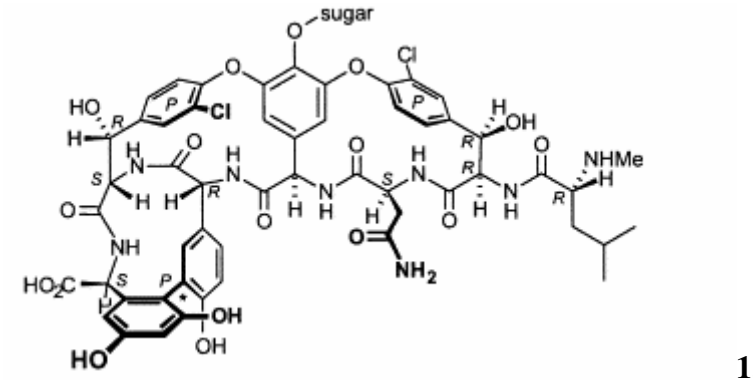
Chapter 1

Introduction

1.1 Introduction

Axial chirality is a term used to refer to steroisomerism resulting from the non-planar arrangement of four groups in pairs about a chiral axis, so that the resulting spatial arrangement is not superimposable on its mirror image. It is exemplified by allenes and by atropisomers, i.e. conformers resulting from restricted rotation about single bonds, where the rotational barrier is sufficient to allow isolation of the enantiopure species (see below). While the stereoselective synthesis of compounds containing one or more stereogenic centers has emerged as one of the most important fields in chemistry, axial chirality, by contrast, has often been overlooked or treated as an "academic curiosity". This, however, has changed with the recognition that the configuration at a biaryl axis can be a decisive factor in governing the pharmacological properties of a bioactive compound[1] and that axial chirality is the fundamental basis for useful reagents and catalysts in asymmetric synthesis.[2]

Natural products equipped with a rotationally hindered biaryl axis are far more widespread and structurally diverse than initially assumed. Many representatives of this class of axially chiral metabolites exhibit remarkable bioactivities, like the famous antibiotic heptapeptide vancomycin (**1.1**).[3] This molecule contains three types of stereoelements- numerous stereogenic centers, two "chiral" planes, and a stereogenic biaryl axis, which together impose the rigid 3D structure necessary for an efficient binding to peptides of bacterial cell walls. Knipholone[4] (**1.2**) possesses solely axial chirality and occurs with varying degrees of enantiomeric purity in nature; compounds of this family of 1-phenylanthraquinones have recently been shown to exhibit good antimalarial and antitumor activities, the latter particularly when a*S* configured Mastigophorene A (**1.3**), a C_2-symmetric bisphenol bearing additional stereogenic centers, has been found to stimulate nerve growth.[5] The class of axially chiral natural products is, however, not restricted to C-C-coupled biaryl compounds. (a*S*)-Murrastifoline-F (**1.4**), for example, is a biscarbazole with the two otherwise identical "halves" connected by a heterobiaryl C-N bond.[6]



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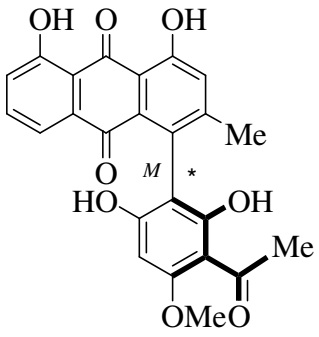
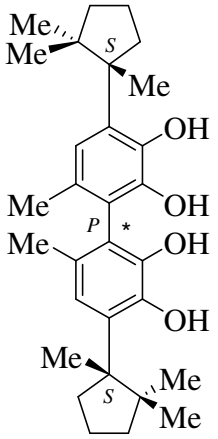
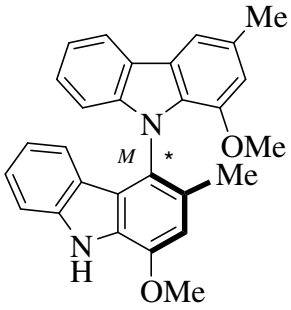


1.2 Knipholone

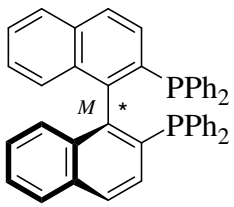


1.3 Mastigophorene

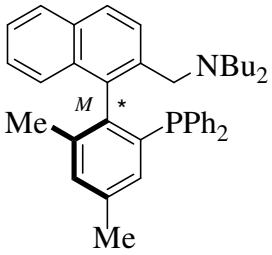


1.4 Murrastifoline-F

Axially chiral biarylic auxiliaries and catalysts exhibit excellent chirality transfer properties.[2] A prime example is the diphosphine BINAP (**1.5**),[7] which is the ligand of choice in Ru-catalyzed asymmetric hydrogenations of C=C and C=O bonds. More recently, attention has been focussed on non-C_2-symmetric biaryl compounds such as the tertiary aminophenol **1.6**, which catalyzes the enantioselective addition of diethylzinc to aldehydes.[8] The isoquinoline-containing phosphine QUINAP (**1.7**) is an example of an axially chiral heteroaromatic biaryl; it has been used as a ligand in Pd-catalyzed asymmetric allylic alkylation reactions.[9]



1.5 BINAP



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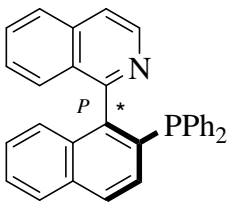
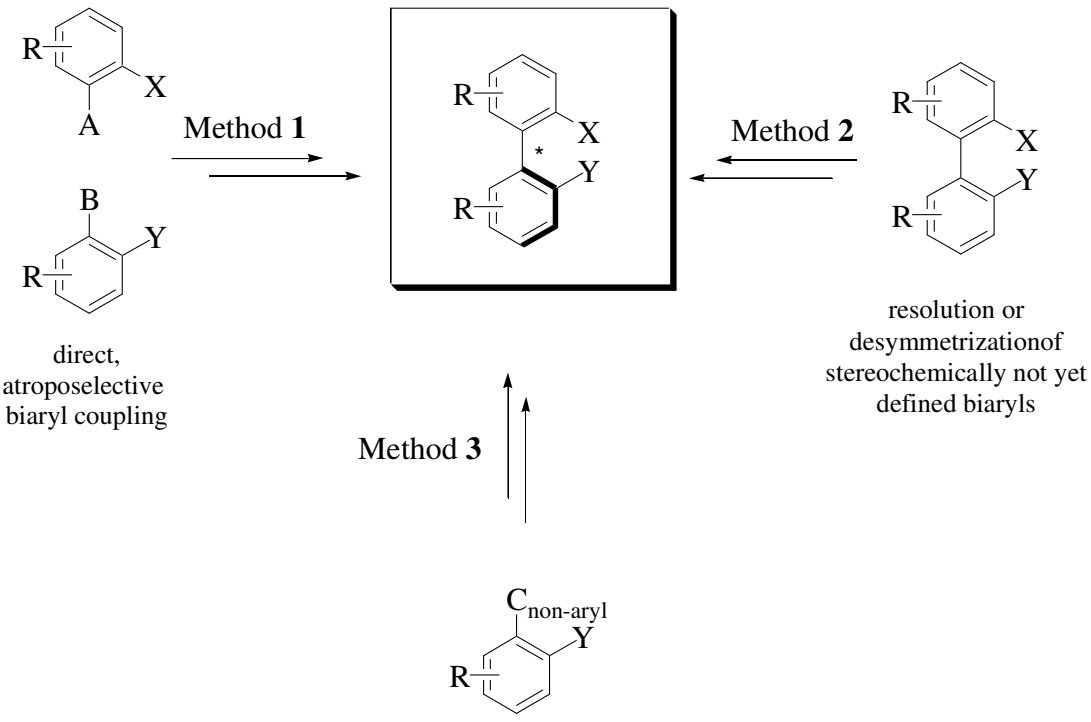


1.7 QUINAP

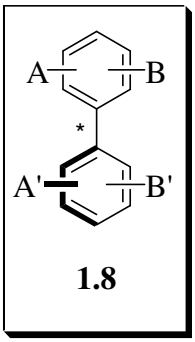
Owing to the importance of axially chiral biaryl compounds, a variety of excellent methods for their directed, atroposelective construction have been developed. The phenomenon of axial chirality relies on the rotational stability of an aryl–aryl single bond. As outlined in the scheme below, three fundamentally different strategies have, to date, been realized for the atroposelective synthesis of axially chiral biaryl compounds.[10] The classic concept, involves biaryl formation in a single step by C-C coupling, with the two aromatic portions being joined with simultaneous asymmetric induction. The second method, by contrast, relies on the atroposelective transformation of an existing, but stereochemically not yet defined, biaryl system. Within this two-step approach, a nonstereoselective coupling step thus precedes the introduction of the stereochemical information at the axis. Finally, the third approach summarizes the few known methods in which a C-C bond between an arene and a precursor substituent is transformed into a chiral biaryl axis by construction of an aromatic ring, usually with a central-to-axial chirality transfer.



1.2. Preconditions for axial chirality and mechanisms of atropisomerization

The phenomenon of axial chirality

Optical activity due to axial chirality has been known since the early 20th century and was first correctly described by Christie and Kenner in 1922. The term "atropisomerism" (from the Greek, a=not and tropos=turn, or in alternative from the name of the fate goddess of the greek and roman mythology Atropos, the inflexible, the fate goddes who cut the thread of human life) was introduced by Kuhn in 1933 and originally referred solely to biaryl compounds. In order to go more in detail, there are two necessary preconditions for axial chirality in biaryl molecules:[11] a rotationally stable axis and the presence of different substituents on both sides of the axis as indicated in **1.8**, that is, A ≠ B and A' ≠ B'. If A=A' and B=B', the molecule has C_2 symmetry (but is still chiral) as in **1.9**, **1.10**, and **1.11**. Surprisingly to the casual observer, even biaryl compounds with four constitutionally identical substituents may be chiral if these are connected pairwise through two bridges as in the D_2-symmetric diether **1.12**. Axially chiral biaryl compounds that bear different *ortho* substituents, such as the dimeric orcinol (**1.9**), are found ubiquitously. Although less common, axial chirality may also result from an inequivalence of meta substituents, as found in the bimesityls **1.10** and in the naphthylisoquinoline alkaloid ancistrocladisine (**1.13**). Furthermore, heteroaromatic systems provide the possibility to introduce chirality merely from the position of the heteroatom, as found in the dipyridyl quateraryl **1.11**.



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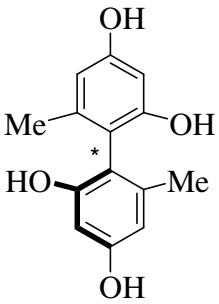

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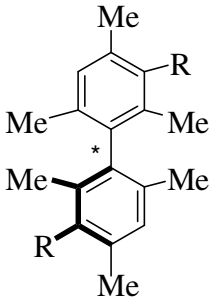
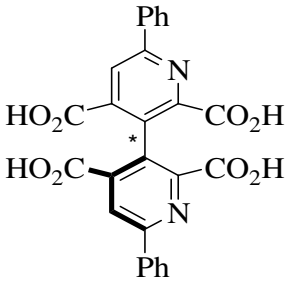


1.10

R = D, NH_2, Br, I



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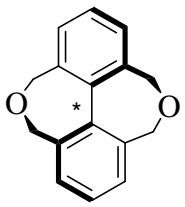

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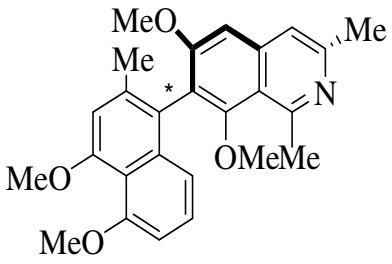
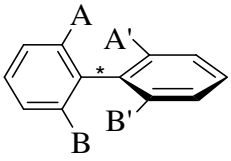
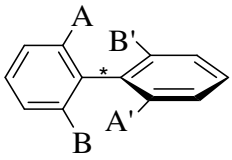


1.13

The absolute axial configuration can be denoted by analysis of a Newman projection along the biaryl axis. After assignment of priority to the *ortho* (or *meta*) substituents according to the CIP rules, the analysis is done by following the shortest 90° path from the substituent of highest priority at the proximal ring to the highest-ranking one at the distal ring (i.e. here from A to A'). If this 90° turn is counterclockwise as in **a**, the absolute configuration is a*S* or *M* (for minus); if it is clockwise as in **b**, then the descriptor is a*R* or *P* (for plus):



a



b

The other crucial precondition for atropisomerism is the rotational stability of the biaryl axis. The temperature has a profound influence: on the one hand, even biaryl compounds with a low degree of steric hindrance will suffer impeded rotation if sufficiently cooled down and split up into atropoenantiomers or -diastereomers if unsymmetrically substituted; on the other hand, biaryl species that are axially chiral at room temperature may start to atropisomerize upon heating, resulting in thermodynamically controlled equilibrium mixtures (i.e. in a full loss of chiral information in the case of enantiomers). As an arbitrary, but useful definition, atropisomers are recognized as physically separable species when, at a given temperature, they have a half-life t of at least 1000 s (16.7 min).[12] Thus the minimum free energy barrier $\Delta G^{\neq}$ required varies with temperature (e.g. $\Delta G^{\neq}_{200K}$ = 61.6 kJmol^{-1},

$\Delta G^{\neq}_{300K}$ = 93.5 kJmol^{-1}, and $\Delta G^{\neq}_{350K}$ = 109 kJmol^{-1}). The configurational stability of axially chiral biaryl compounds is determined by three major factors: 1) the (combined) steric demand of the substituents in proximity to the axis; 2) the existence, length, and rigidity of bridges; and 3) the involvement of atropisomerization mechanisms different from a merely physical rotation about the axis, for example, by photochemically or chemically induced processes.

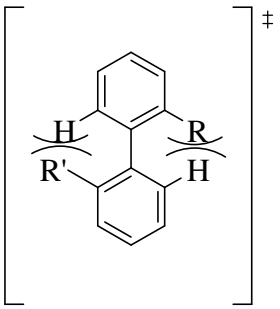
1.3 Atropisomerization by physical rotation

Physical—that is, thermal—rotation about a biaryl axis has, in selected cases, been shown by quantum-chemical calculations to occur through twisted (i.e. non planar) transition states in which the bonds to the *ortho* substituents and the aryl rings are distorted, thus permitting the substituents to pass each other more easily than in a rigid planar transition state. In many cases, the barrier to rotation can be rationalized in terms of substituent effects.

1.3.1 Effects of Nonbridging Substituents

ortho-Substituents increase the atropisomerization barrier in nonbridged biaryl compounds by their steric repulsion (compare **1.14** and **1.17**), corresponding largely to the van der Waals radii of the substituents, that is, I>Br>Me>Cl>NO_2>CO_2H>OMe>F>H. Open-chain (i.e. nonbridged), mono-*ortho*-substituted biaryl compounds do not form stable atropisomers at room temperature. With two substituents next to the axis, atropisomerism at room temperature is only observed if both groups are bulky, as in 1,1'-binaphthyl (**1.15**) and in 2,2'-bis(trifluoromethyl)biphenyl (**1.16**), so that in the transition state **1.14** even the interactions of R and R' with the small hydrogen atoms provide sufficient steric repulsion for restricted rotation. As a rule, tri-*ortho*-substituted biaryl compounds form stable atropisomers; in the transition state **1.17**, two substituents now must pass one another for rotation to occur, rather than a substituent passing a hydrogen atom. The biphenyl **1.18** is an example of such an axially chiral biaryl system. Nevertheless, sterically less demanding substituents may still permit slow axial rotation as observed with the naphthylisoquinoline alkaloid dioncophylline E (**1.19**), whose atropisomerization occurs within a few hours at room temperature. Conformational stability is virtually guaranteed for tetra-*ortho*-substituted biaryl compounds, even if the

substituents are all small, as in the tetrafluorobiphenyl **1.20** ($\Delta G^{\neq}_{358K}$ =108 kJmol^{-1}). The rotational barriers can be extremely high, as in the auxiliary binol (**1.21**, $\Delta G^{\neq}_{493K}$ = 158 kJmol^{-1}), making these compounds configurationally stable even under forcing conditions; in many cases the atropisomerization temperature is so high that it cannot be reached without decomposition. Ancistrocladine (**1.22**), as an example, can be dehydrogenated at 200° C without loss of atropisomeric purity; at higher temperatures, the molecule disintegrates.



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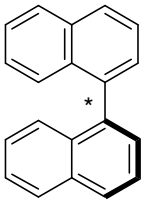

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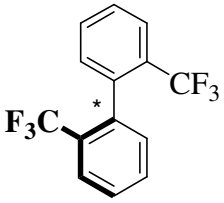

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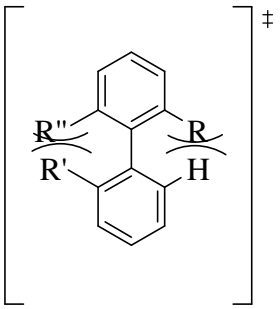

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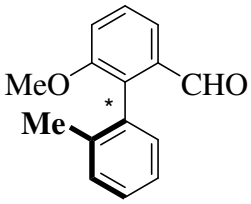

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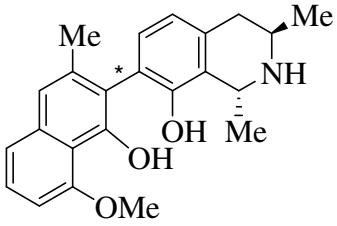

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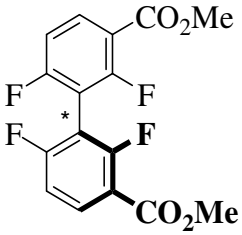

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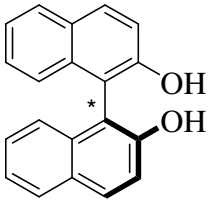

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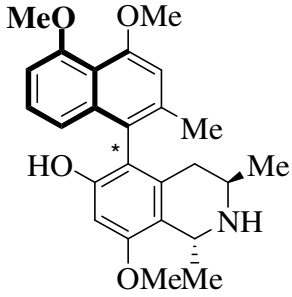
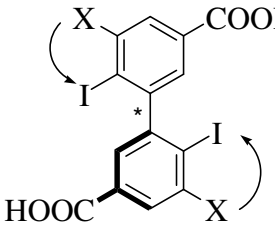


1.22

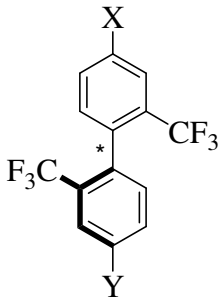
Bulky substituents in the *meta* positions increase the configurational stability of biaryl compounds by "buttressing" the *ortho* substituents, thus preventing their bending out of the way in the transition state. For example, rotation in the tetraiodobiphenyl **1.23b**

(Figure 6) is considerably more difficult than in its diiodo analogue **1.23a** ($\Delta G^{\neq}_{298K}$ = 126 kJmol^{-1} vs. $\Delta G^{\neq}_{298K}$ = 98 kJmol^{-1}). *para* Substituents influence the rotational barrier mainly by electronic effects, as evidenced by the 4,4'-substituted biphenyls **1.24**. Electron donation by resonance from the substituent at C4 increases the sp^3 character at C1, thus facilitating the out-of-plane bending at these positions. This decreases the strain in the transition state and, therefore, lowers the barrier to rotation (**1.24**(**b–e**)). By the same token, electron-withdrawing groups, which restrict the out-of-plane bending by decreasing the electron density at C1, raise the barrier (**1.24 f**,**g**).



1.23

a: X = H
b: X = I

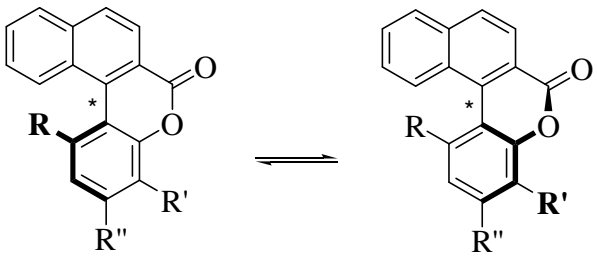


1.24

a: X = H; Y = H
b: X = NH_2, Y = NH_2
c: X = OMe, Y = OMe
d: X = NH_2, Y = H
e: X = OMe, Y = H
f: X = NO_2, Y = H
g: X = NO_2, Y = NO_2

1.3.2. Bridged Biaryl Systems

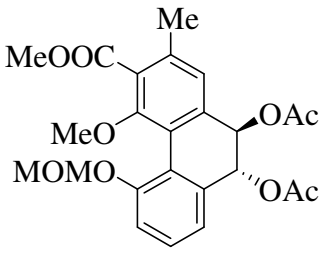
The effect of a bridging ring on the restricted rotation of a biaryl system varies greatly with the ring size. In systems in which two of the *ortho* substituents are replaced by a single bridging atom (i.e. a five-membered ring is formed), rotation is usually not hindered at room temperature. The presence of a six-membered bridge still considerably facilitates rotation, but to a lesser extent. A comparative study was done on the benzonaphthopyranones **1.25** and **1.26**, which exist as racemic mixtures of their helically distorted atropoenantiomers (a*S*)- and (a*R*)-**1.25** and -**1.26**. $\Delta G^{\neq}_{298K}$ increases with the steric demand of the ortho substituent R.



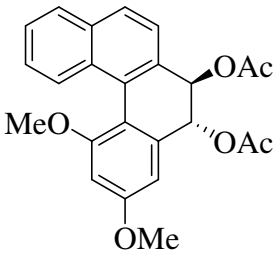
(a*S*)-**1.25** (a*R*)-**1.26**

Thus, the compounds atropisomerize quickly at room temperature when R=H, OMe, Me, Et with half-lives τ_{298K}<1 min, whereas when R = *i*Pr is at the brink of atropisomerism (τ_{298K} =28 min). The enantiomers of the largely distorted derivative with R = *t*Bu are configurationally stable and can be resolved by both physical and chemical methods.

Stereogenic centers in the bridge can strongly influence the—now atropodiastereomeric—equilibrium as, due to the exocyclic substituents (axial or equatorial), the bridge adopts the thermodynamically favorable conformation. For example, the biaryl compounds **1.27** and **1.28** are configurationally unstable at room temperature, and occur as 1:1 mixtures of atropodiastereomers, despite the presence of two stereogenic centers in the bridge, whereas **1.29**, with the dioxolane system enforcing a di-equatorial conformation, exists as a single diastereomer.



1.27



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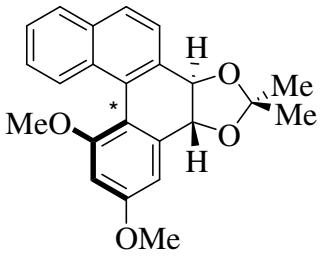
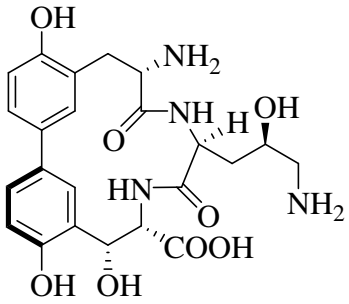


1.29

Biaryl compounds containing seven-membered rings exhibit rotational stabilities almost comparable to those of their unbridged analogues. Larger bridges, including those formed by hydrogen bonding, can induce atropisomerism by geometrical constraints of the ring, even in biaryl systems with relatively little axial hindrance. An example is the tripeptide antibiotic biphenomycin A **1.30** which does not have any *ortho* substituents next to the axis, occurs as a single atropodiastereomer.[71] It is, however, not clear

whether **1.30** is conformationally stable (high barrier) or, rather, labile with the atropodiastereomeric equilibrium completely shifted towards that isomer (thermodynamic effect).



1.30

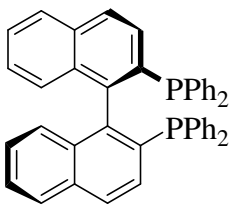
1.4. Diphosphine ligands

1.4.1. BINAP in asymmetric catalysis

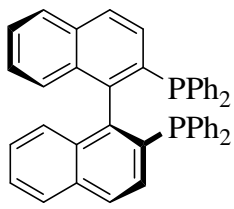
The use of atropisomeric binaphthyls as chiral auxiliaries in asymmetric synthesis has previously been reviewed by Salvadori in 1992 and Pu has reviewed atropisomeric binaphthyl dimers, oligomers and polymers in molecular recognition, asymmetric catalysis and novel materials in 1998.[13,14]

2,2'-Substituted 1,1'-binaphthyls are particularly good of chiral ligands for asymmetric catalysis. Their conformational flexibility about the binaphthyl C(1)-C(1') pivot allows a range of bite angles to accommodate a wide variety of transition metals.

In fact, the most well-known example of an axially chiral ligand is the diphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) **1.31**, a C_2-symmetric triaryldiphosphine (Scheme 1), the synthesis and fist application of which were reported by Noyori and Tanaka in 1980:[7]



1.31 (*R*)-BINAP

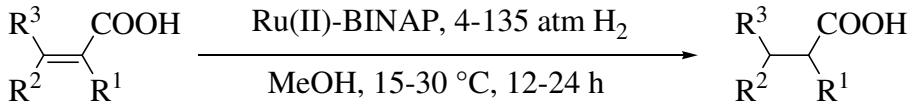


1.31 (*S*)-BINAP

This ligand very effectively induces asymmetry by intra-complex steric interactions between the bulky triarylphosphine system and the reactants bound to the metal. Its application in asymmetric catalysis has been reviewed in 1990 and 1992 and subsequently its use has been well documented in numerous textbooks.

Only a summary of its applications before 1992 will therefore be detailed here and an emphasis will be placed on its more recent success.[2]

Up to and including 1992, ruthenium complexes of BINAP **1.31** had proved to be successful in inducing high to excellent enantioselectivities in the hydrogenation of olefinic substrates, such as a range of α,β-unsaturated carboxylic acids **1.32**.

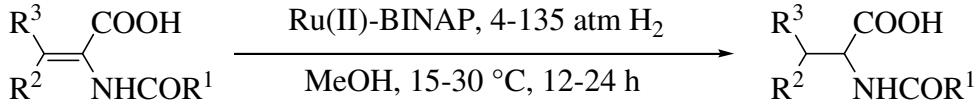


1.32

85-89% *ee*

R^1 = alkyl, aryl, hydroxycarbonylalkyl
R^2 = H, hydroxyalkyl
R^3 = H, alkyl

N-acylaminoacrylic acids **1.33** were successfully reduced using Ru(II)-BINAP and Rh(I)-BINAP complexes in high to excellent enantioselectivities. The scope of Rh(I)-BINAP catalysis is, however, limited to a small range of suitably functionalised olefin substrates Ru(II)-BINAP chemistry has a broad utility.

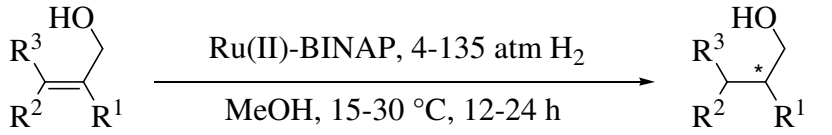


1.33

up to 100% *ee*

R^1 = alkyl, aryl
R^2 = H
R^3 = H, alkyl, aryl

Highly enantioselective reduction of substituted allylic alcohols **1.34** has also been achieved With the latter substrates, the sense and extent of asymmetric induction are highly dependent on the substitution pattern and the reaction conditions, in particular the hydrogen pressure employed.



1.34

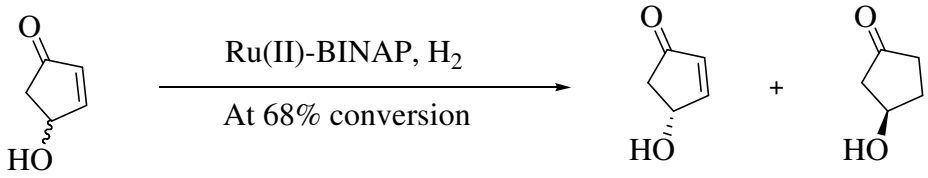
R^1 = alkyl, aryl

R^2 = H

R^3 = H, alkyl, aryl

up to 99% *ee*

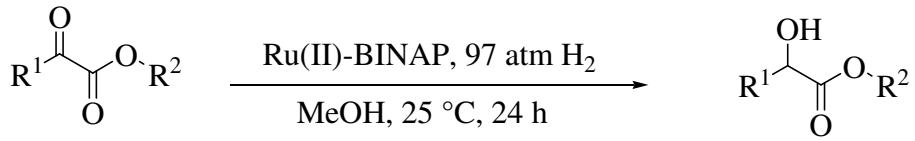
Racemic allylic secondary alcohols, e.g. 4-hydroxy-2-cyclopentenone **1.35**, were successfully resolved by a kinetic resolution process using BINAP-Ru-catalysed hydrogenation.



1.35

98% *ee*

As with olefin hydrogenations, the application of BINAP-Ru complexes to the enantioselective reduction of carbonyl groups had reached a high level of success by 1992. α-Keto acid **1.36** derivatives were reduced in quantitative yields with enantioselectivities of up to 89%.



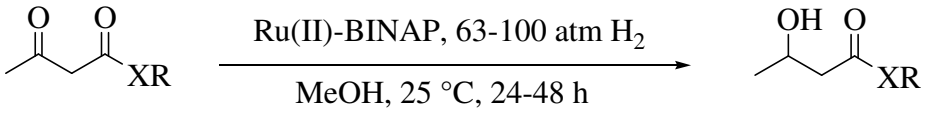
1.36

R^1 = alkyl, aryl

R^2 = alkyl

100%, 89% *ee*

Similarly, excellent reactivities and enantioselectivities were obtained with β-keto esters **1.37** as the substrates. The asymmetric reduction of 1,3-dicarbonyl systems with Ru-biarylphosphine catalysts was reviewed by Ager in 1997.

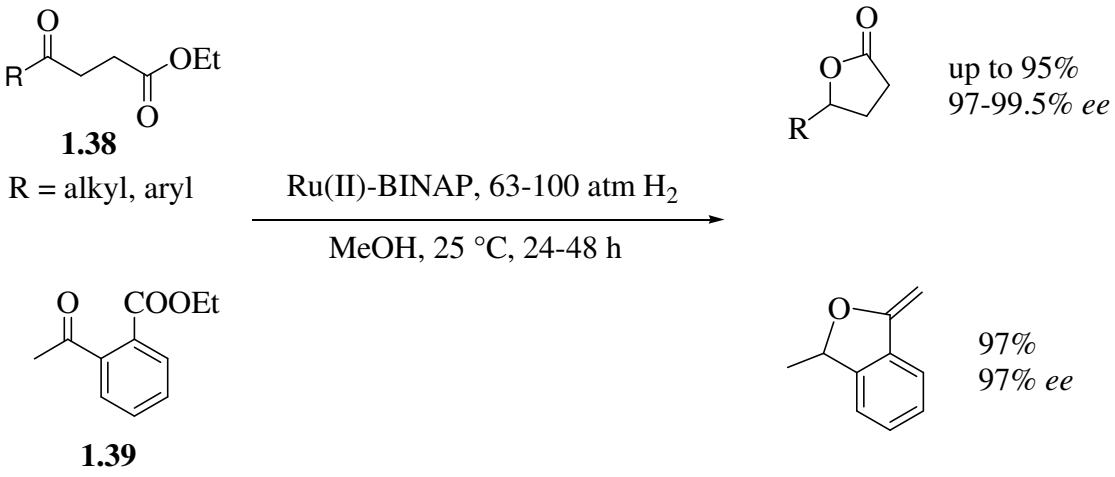


1.37

R = alkyl
X = O, NR, SR

95-100%
93->99% *ee*

The hydrogenation of γ-keto **1.38** esters and *o*-acylbenzoic esters **1.39** by BINAP-Ru complexes affords the corresponding γ-lactones or *o*-phthalides in excellent enantioselectivities:

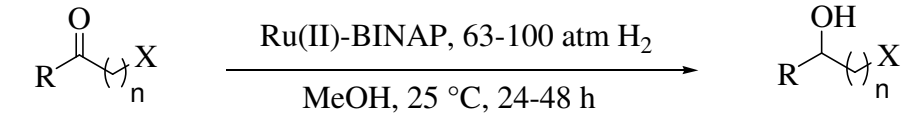


1.38

R = alkyl, aryl

1.39

Other successful substrates for BINAP-Ru catalysed enantioselective reduction include amino and hydroxyl ketones **1.40**:

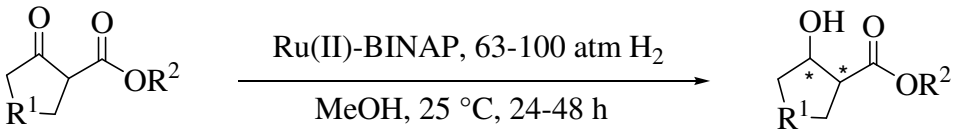


1.40

R = alkyl, aryl
X = OH, NR_2
n = 1-2

85-100%
95-99% *ee*

A particularly efficient dynamic kinetic resolution of the α-substituted β-keto esters **1.41** using BINAP-Ru catalysis has also been developed, where >95% yield of one of the four possible diastereomeric esters is obtained in excellent enantiomeric and diastereomeric excess.

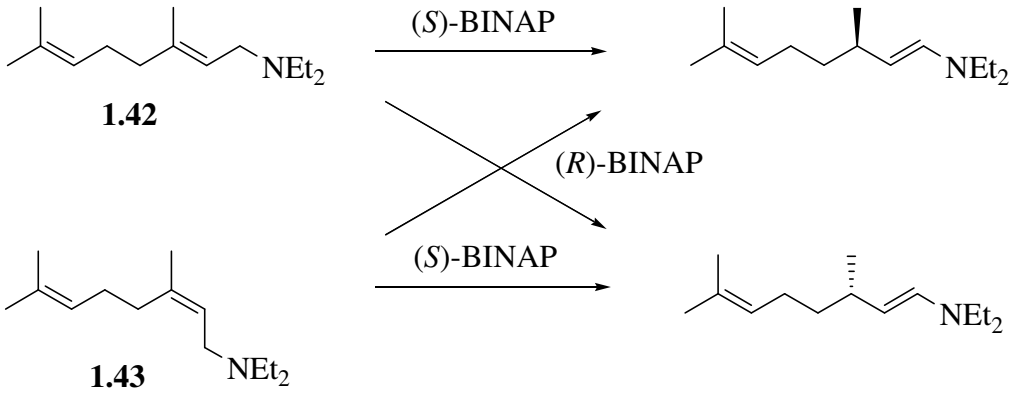


1.41

$R^1 = CH_2, (CH_2)_2, (CH_2)_3$
R^2 = Me, Et

anti/*sin* = 97/3 to 99/1
92-99% *ee*

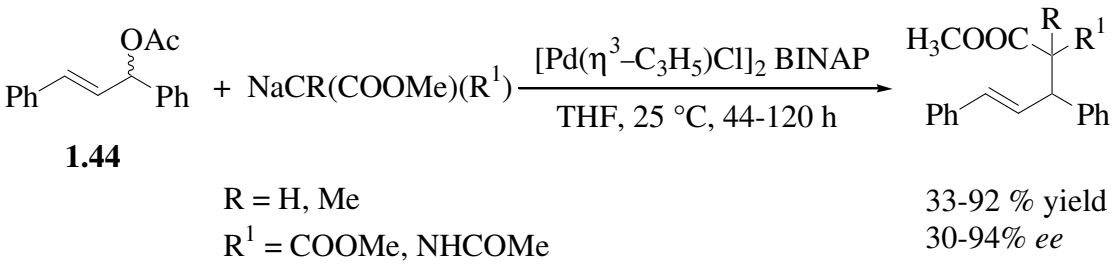
The BINAP-Rh catalysed enantioselective isomerisation of the allylamines **1.42** and **1.43** to optically active enamines proceeds with high chemoselectivity and excellent enantioselectivity (96-99%). In this asymmetric isomerisation there is an excellent correlation between the substrate geometries, product (*E*)-enamine configurations and the BINAP chirality.



1.42

1.43

The enantioselective substitution of allylic acetates is the most studied asymmetric carbon-carbon bond forming process catalysed by transition metal complexes of palladium. It is an important transformation and has proved to be a useful testing ground for the design and testing of novel ligands and for gaining mechanistic insights into organopalladium chemistry. Pd complexes of BINAP were applied with some success to the standard test reaction of malonates and 1,3-diphenylpropenyl acetate **1.44**. The reaction times were relatively long and enantioselectivities and chemical yields were moderate to good.

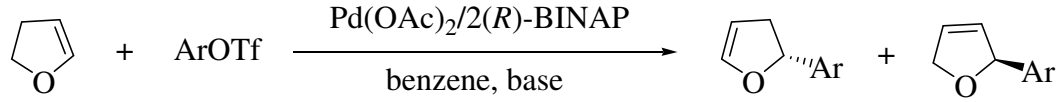


1.44

R = H, Me
R^1 = COOMe, NHCOMe

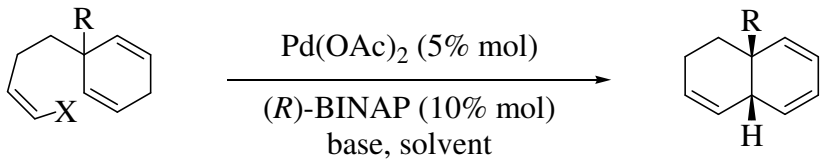
33-92 % yield
30-94% *ee*

A second carbon-carbon bond forming reaction to which palladium complexes of BINAP have been studied is the Heck reaction. In the intermolecular variant, the test reaction is between 2,3-dihydrofuran **1.45** and the aryl triflates **1.46**. Ref. Hayashi reported that this reaction, which proceeded in the presence of a base and a palladium catalyst generatd in situ from $Pd(OAc)_2$ and (*R*)-BINAP, gave the (*R*)-2aryl-2,3-dihydrofuran **1.47** and a small amount of the (*S*)-2-aryl-2,5-dihydrofuran **1.48**. The base affected the enantiomeric purity of (*R*)-**1.47** and the sterically demanding 1,8-bis(dimethylamino)naphthalene (proton sponge) afforded the best results for a range of aryl triflates.



1.45 **1.46** (R)-**1.47** (S)-**1.48**

The first successful intramolecular asymmetric Heck reactions using BINAP-Pd complexes were reported in 1989 by Shibasaki who focused on the preparation of the *cis*-decalin derivatives **1.49** from the prochiral alkenyl iodides or triflates **1.50** and obtained enantioselectivities of up to 92% in moderate chemical yields of 60%.

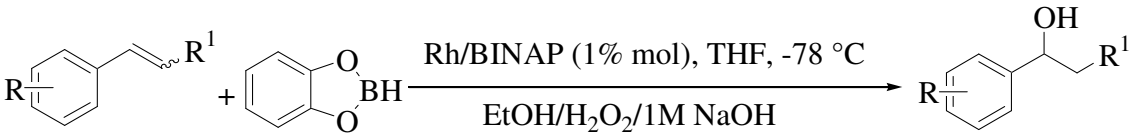


1.50 **1.49**

R = COOMe, CH_2OAc, $CH_2OTBDMS$
X = I, OTf

up to 92% *ee*

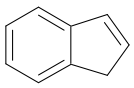
The hydroboration of vinylarenes, catalysed by cationic Rh(I)-phosphine complexes, has become a transformation of significant importance. One of the first enantioselective variants was developed by Hayashi who employed Rh-BINAP complexes for hydroboration of the styrenes **1.51** in *ees* up to 96%.[15] Cyclic vinylarenes, such as indene **1.52** and dihydronaphthalene **1.53**, were poor substrates as only 19% *ee* was obtained with **1.52**, whereas no reaction was reported for **1.53**.



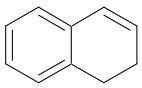
1.51

R = H, Me, MeO, Cl
R^1 = H, Me

ees up to 96%



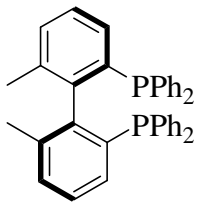
1.52



1.53

After the success of BINAP it is not surprising that the synthesis and design of other atropisomeric diphosphines became an attractive area of research in the late 1980s and continues to the present day. The electronic properties at phosphorus were the first variation to be investigated and this led to the preparation and application of a series of BINAP analogues, which retain the 1,1'-binaphthyl backbone but differ in the bis-arylphosphine group. Some of these examples are presented in Chapter 3.

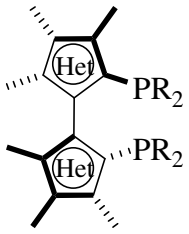
The biphenyl system is easier to modify geometrically, sterically or electronically than the binaphthyl system, leading to the synthesis of a variety of atropisomeric biphenyl diphosphines and the application of their metal complexes in asymmetric catalysis. The group of Schmid and Frejd have independently prepared 2,2'-bis8diphenylphosphino)-6,6'-dimethyl biphenyl **1.54** (BIPHEMP) and the related analogues.[16,17]



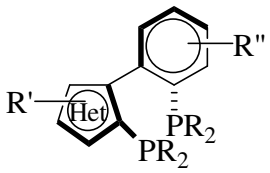
1.54 BIPHEMP

As the biphenyl group, like the binaphthyl group, is not completely rigid it can form a variety of stable chlate complexes with many transition metals. It was, however, necessary to substitute the 6,6'-positions in order to prevent racemization. Some other examples of biphenyls ligands are discussed in Chapter 3.

Another interesting class of ligands are the chelating diphosphines supported on stereogenic atropisomeric biaryl scaffolds, containing heteroatoms such as **1.55** and **1.56**. The electron density at the donor centers of these ligands is a crucial parameter controlling both reaction kinetics and stereoselectivity.[18]



1.55



1.56

The nature of the heterocyclic system constituting the backbone, and the position of the diphenylphosphino groups, strongly influence the electronic properties at phosphorus, which ranges gradually from very electron poor to very electron rich situations.[19,20]
Sannicolò et *al*. reported the synthesis, resolution and X-ray analyses of several ligands and transition metal complexes belonging to this familiy, which were used as ligand in some Ru, Rh, and Pd homogeneous catalysis experiments.

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